British Journal of Psychiatry (1985), **146,** 377–382

Changes in the Diagnoses of the Functional Psychoses Associated with the Introduction of Lithium

GORDON PARKER, MARYANNE O'DONNELL and STEPHEN WALTER

Summary: Diagnostic patterns for schizophrenia and affective psychosis were examined for all admissions to psychiatric facilities in New South Wales over a ten-year (1967–1977) period, before, during, and after lithium carbonate had been established as an accepted treatment. While the proportion of functional psychoses to total admissions remained relatively constant over the study, there was a relative decrease in schizophrenia, and a relative increase in the affective psychosis group. Analyses of sub-groups suggested, after controlling for the effects of time, that the introduction of lithium has been associated with an increase in diagnoses of mania and a decrease in diagnoses of paranoid schizophrenia, both for first admissions and for readmissions.

The prophylactic action of lithium carbonate in manic-depressive illness has been established in extensive trials (Schou, 1983). Symonds & Williams (1981) suggested that the introduction, and increased use, of such an effective treatment should have resulted in a profound decrease in admissions, and particularly readmissions of those with mania. They investigated age-standardised admission rates from England for the years 1970–75, when there was a marked change in the use of lithium, although they acknowledged that ideally, the data for the period before the introduction of lithium should have been examined. For first admissions, they found a significant linear decrease in the total number, but no such trend for mania, with the proportion of male admissions for mania actually rising. The total number of readmissions increased over the same period, and female manic patients showed a significant increase in readmissions over that interval. Three possible hypotheses were suggested: a biological change in the nature of the illness, a decrease in tolerance by society to disturbed behaviour, and a change in diagnostic fashion.

The last possibility was alluded to by Cade (1979), who stated that "if treatment for a specific condition is dramatically successful there is a marked tendency to over-diagnose it". Such a phenomenon has also been noted by Baldessarini (1970), who studied diagnosis patterns in a university psychiatric clinic from 1944 to 1968, noting that the introduction of phenothiazines was associated with an increase in the number of diagnoses of schizophrenia, and of lithium with an increase in the number of diagnoses of affective psychosis. The possible extent to which such a phenomenon may be associated with the introduction of lithium is suggested in a study by Horgan (1981); he studied 36 patients admitted to the Royal Edinburgh Hospital between 1970 and 1977 with an operationally confirmed diagnosis of mania, and who had previously been diagnosed as having a non-affective illness. He found that half had received a previous diagnosis of schizophrenia. While both these studies are thought-provoking, the possibility is raised that only individual and parochial changes in diagnostic fashion has been detected, since they were conducted at single clinical units. A wider study of a region or country is clearly required.

We undertook such a study in New South Wales to assess diagnostic changes associated with the introduction of lithium. In view of Horgan's findings and supportive clinical observations, we limited data collection to schizophrenia and the affective psychoses, with the premise that any change in the diagnosis of affective psychoses would be reflected in changes in the relative proportion of the two groups. We further sought to determine those sub-groups of the functional psychoses showing the greatest relative and meaningful variation in diagnostic allocation over time, since such information might suggest those diagnoses most subject to diagnostic ambivalence. Kendell *et al* (1971) noted that, as the majority of patients do not fit neatly into well defined diagnostic categories, in practice, every classification has to have loosely defined categories for patients who cannot be accommodated elsewhere. Thus, we further sought to determine whether the introduction of lithium has been associated with any change in the numbers receiving a diagnosis of schizo-affective psychosis,

TABLE I

Lithium dispensed in New South Wales over the three study phases

Phase		*National Health Service Prescriptions in NSW*	*Quantity dispensed in NSW (tons)*
'Pre-lithium'	1967–71	—	—
'Early lithium'	1971–72	349	0.05
	1972–73	2141	0.08
	1973–74	4552	0.26
'Established lithium'	1974–75	8657	0.45
	1975–76	17306	0.73
	1976–77	20140	0.82

since that diagnosis is used by many clinicians for classification of psychotic disorders showing features both of affective psychosis and schizophrenia.

Method

Data for New South Wales were obtained from the Australian Bureau of Census and Statistics, which records details of all admissions to State psychiatric hospitals, psychiatric units of general hospitals, and most admissions to private psychiatric hospitals. Recorded data are neither sex-specific nor age-standardised. First admission and readmission data were collected for the ICD 8 diagnostic categories for schizophrenia and affective psychosis, commencing in July 1967 and ceasing in June 1977, as the introduction of ICD 9 in 1978 might have, in itself, brought about changes in the recording of diagnoses.

Schizophrenic sub-groups were preserved in the data tabulation, except when numbers were small. Thus, the 'remainder' sub-group (see tables II and III) represents 'hebephrenic', 'catatonic', 'latent', and 'residual' schizophrenia. 'Other' schizophrenia refers to types not classified elsewhere, including chronic undifferentiated schizophrenia. Similarly, the 'remainder' sub-group of the affective group represents those allocated 'involutional melancholia', 'manic depressive psychosis, circular type', 'other' and 'unspecified' diagnoses, with unaggregated numbers being, in several cases, quite small.

Admission data were grouped. The four year 'pre-lithium' period ranges from July 1967 to June 1971, and precedes the introduction of lithium carbonate as a pharmaceutical product in December 1971. July 1971 to June 1974 represents the 'early-lithium', and July 1974 to June 1977 represents the 'established lithium' phase.

The Commonwealth Department of Health provided data on prescriptions dispensed by chemists in New South Wales, while data on the quantity dispensed in the State were obtained from the one pharmaceutical company dispensing it there. Table I reports those data, the simple correlation between the two measures of dispensed lithium being + 0.99, and the number of lithium prescriptions was used as the predictor variable in the analyses.

Results

Table II reports data on first admissions over the three study periods. After correction is made for the unequal periods, the proportion of the combined schizophrenia and affective ('combined functional') psychoses to total first admissions remains relatively constant at 18% to 20%. Within the 'combined functional' group, the schizophrenia percentage decreases, while the affective psychosis percentage increases by 3.3% ($\chi^2 = 14.19$, df 2, $P < .001$). Percentage changes for each diagnosis from the

TABLE II

First admissions by diagnosis and lithium phase

Diagnosis	*ICD No.*	*'A' 'Pre-lithium' 1967–71*	*'B' 'Early lithium' 1971–74*	*'C' 'Established lithium' 1974–77*	*Change from 'A' to 'C'**
Schizophrenia		4251	3389	2904	−9%
Paranoid	295.3	1856	1412	1087	−22%
Acute	295.4	601	472	400	−11%
Schizoaffective	295.7	195	100	113	−22%
Unspecified	295.9	756	639	758	+34%
Other	295.8	330	461	342	+38%
Remainder	295.0, .1, .2, .5, .6	513	305	204	−47%
Affective		2082	1694	1646	+5%
MDP-mania	296.1	264	290	268	+35%
MDP-dep	296.2	1491	1203	1178	+5%
Remainder	296.0, .3, .8, .9	327	201	200	−18%
Schizophrenia and affective ('Combined functional')					
Schizophrenia		67.1%	66.7%	63.8%	
Affective		32.9%	33.3%	36.2%	
Total and percentage of all diagnoses		6333 (18%)	5083 (19%)	4550 (20%)	−4%
All other diagnoses		28164	21319	18546	−12%

*Examining for change within each key group (i.e. schizophrenia and affective) after correcting for unequal period lengths.

'pre-lithium' to the 'established lithium' period are reported in Table II, but are difficult to interpret, being based on crude admission numbers and ignoring variations of numbers in the base population. Inter-group comparisons were therefore made. Most of the chi-square tests were highly significant, generally demonstrating associations because of the large sample sizes involved. For that reason, phi coefficients were calculated, as they quantify the proportion of the variation in the distribution of diagnoses which might be explained by or associated with temporal effects. Changes in first admission diagnoses were evaluated in all six categorised sub-groups of schizophrenia, and were clearly significant ($\chi^2 = 205.6$, df 10, $P < .001$) with a phi coefficient of 14%. The sub-groups showing the clearest change within the whole schizophrenia group were 'paranoid' (decreasing from 44% to 39%), the 'remainder' (decreasing from 12% to 7%), and 'unspecified' (increasing from 18% to 27%). Changes in first admission diagnoses for the three categorised affective psychosis sub-groups were less marked ($\chi^2 = 27.3$, df 4, $P < .001$), the phi coefficient being 7%, with the sub-group 'mania' showing an increase (from 13% to 16%) and 'other' a decrease (from 16% to 12%). The proportion of schizo-affective diagnosis, in relation to the 'combined functional' group, remained relatively constant at 2% to 3% over the three periods.

Table III reports data on readmissions. As for first admissions, the proportion of 'combined functional' to all readmissions remains relatively constant at 31% to 33% across the three study periods. Within the 'combined functional' group, the schizophrenia percentage decreases, while the affective psychosis percentage increases by 6.0% ($\chi^2 = 143.1$, df 2, $P < .001$). Percentage changes for each diagnosis from the 'pre-lithium' to the 'established lithium' period suggest a more marked increase in affective, rather than in the schizophrenia sub-groups, but such data are difficult to interpret, as noted above, and inter-group comparisons are more appropriate. Changes in readmission diagnoses were marked within the six categorised sub-groups of schizophrenia ($\chi^2 = 1069.6$, df 10, $P < .001$), the phi coefficient being 18%. The sub-groups showing the clearest change were 'paranoid' (decreasing from 40% to 31%), the 'remainder' (decreasing from 13% to 7%), and 'other' (increasing from 15% to 29%). Changes in readmission diagnoses for affective psychosis sub-groups were also significant ($\chi^2 = 32.8$, df 4, $P < .001$, phi 5%), with 'mania' showing an increase (from 19% to 24%), 'depression' a decrease (from 61% to 56%), while the 'remainder' remained relatively constant. The proportion of schizo-affective diagnoses, in relation to the 'combined functional' group, changed marginally over the study periods from 5%, to 3%, to 4% respectively.

These analyses demonstrate changes between, and within each of the functional psychotic groups. The degree to which there has been a 'spill' from one diagnostic group to another cannot be estimated by the present study design but, on the basis of consistency across first admissions and readmissions, and on there being meaningfully large numbers for analysis, we suspect a spill from 'paranoid schizophrenia' to 'mania'. For first admissions, the ratio of 'mania' to 'paranoid schizophrenia' rose progressively from .14 in the 'pre-lithium' period, to .20 in the 'early lithium' period, and to .25 in the 'established' lithium period. For readmissions, the ratios showed an even more impressive increase from .12 to .19 to .30 respectively.

Further analysis was carried out using product moment correlations (r) to evaluate the relationships between

TABLE III

Readmissions by diagnosis and lithium period

Diagnosis	*'A' 'Pre-lithium' 1967–71*	*'B' 'Early lithium' 1971–74*	*'C' 'Established lithium' 1974–77*	*Change from 'A' to 'C'**
Schizophrenia	11640	9459	11101	+27%
Paranoid	4638	3458	3468	−0%
Acute	413	407	427	+38%
Schizoaffective	705	439	687	+30%
Unspecified	2632	1512	2519	+28%
Other	1785	2702	3251	+143%
Remainder	1467	941	749	−32%
Affective	3342	3246	4375	+75%
MDP-mania	647	658	1048	+116%
MDP-depressed	2041	1920	2434	+59%
Remainder	654	668	893	+82%
Schizophrenia and affective ('Combined functional')				
Schizophrenia	77.7%	74.4%	71.7%	
Affective	22.3%	25.6%	28.3%	
Total and percentage of all diagnoses	14982 (32.6%)	12705 (30.6%)	15476 (32.1%)	+38%
All other diagnoses	30926	28810	32660	+41%

*Examining for change within each key group (i.e. schizophrenia and affective) after correcting for unequal period lengths.

admission frequencies in individual years and lithium prescriptions in those years; for comparison, we also computed the correlations between admission frequencies and year, to assess secular effects. We found that first admission diagnoses of schizophrenia declined (non-significantly) over the period (r = −.43), but were significantly related to the increase in lithium prescriptions (r = −.79). By contrast, schizophrenia readmissions increased significantly over time (r = +.94), and correlated positively with the increase in lithium prescriptions (r = +.94). Affective psychosis diagnoses increased over time, more dramatically for readmissions (r = +.94) than for first admissions (r = .29, not significant), while the increase in lithium prescriptions correlated with increased readmissions (r =+.94) but not with first admissions (r = −.06).

Because lithium prescriptions have increased progressively over time, these correlational analyses would be expected to show similar relationships between a given frequency of admission and either lithium or year. As variation in the lithium prescriptions is the variable that interests us most, multiple regression analyses were undertaken assessing for the two factors (lithium prescriptions and year) simultaneously, so that the effects of lithium and time could be mutually adjusted for the effect of the other. Table IV shows that neither time nor lithium prescriptions influenced total schizophrenia first admissions, and we assume that, as both predictors were negatively associated with admissions, they confounded each other, preventing separation of the two effects. For schizophrenia readmissions, time is significant, but any lithium effect is just short of significance ($P = .06$), and we assume a similar confounding influence. For affective psychosis first admissions, both time and lithium have significant effects, perhaps as a consequence of the opposite directions of their simple associations. For affective psychosis readmissions, time is significant, but lithium falls short of significance ($P = .07$), and once again, confounding of the predictors may have occurrred. A similar regression analysis was conducted for the paranoid schizophrenia sub-group. Adjusted for time, a significant negative relationship was found for lithium, both in relation to first admissions (Beta = −0.004, $P < .05$) and readmissions (Beta = −.014, $P < .05$).

Finally, the data for 'mania' were analysed in two slightly differing regression analyses. When total affective psychoses and lithium were entered as independent variables, lithium was a significant predictor of readmissions (Beta = 0.007, $P < .05$), but not of first admissions. When total schizophrenia was added as an additional independent variable, lithium was the only significant predictor of mania readmissions (Beta = 0.009) while, for mania first admissions, total schizophrenia numbers (Beta = 0.26, $P < .05$) and lithium (Beta = 0.003, $P < .05$) were both significant predictors.

TABLE IV

Results of regression analyses examining for effects of lithium and time, mutually adjusted for each other, on key diagnostic groupings

		Beta values	
Diagnosis	*Admission*	*Time*	*Lithium*
Schizophrenia (total)	First admission	.09	−0.003
	Readmissions	.12**	.016
Affective (total)	First admission	.10*	.007*
	Readmissions	.80*	.017

* $P < .05$
** $P < .01$

Discussion

In examining the proposition that the introduction of lithium may, in itself, have had an influence on diagnostic patterns, there is a clear need to demonstrate the accuracy of the predictor variable. We obtained data on the dispensation of lithium over time in New South Wales from two sources, demonstrated a very high correlation between the two independent measures, and therefore have some confidence in our predictor variable. While we demonstrated a relative increase over the three periods of 27% for schizophrenia diagnoses and 75% for affective diagnoses, the degree to which these might reflect actual increases in the numbers of patients receiving a particular diagnosis or increases in the number of admissions per patient over the study period was not established. As it is conceivable that the introduction of a successful treatment might differentially influence both first admission and readmission diagnoses, we sought to assess effects on readmissions in general, rather than on first admissions only.

Over the ten-year period 1967–1977, corresponding with the introduction of lithium in New South Wales, and while the proportion of schizophrenia and affective psychoses out of the total admissions remained relatively constant, the schizophrenia percentage decreased at the expense of the affective psychoses by 3% for first admission and by 6% for readmissions, suggesting some spill from the former to the latter diagnostic group. Over the three periods of interest, changes were demonstrated, both between and within each of these two broad groups. We rejected the strategy of examining all proportional diagnostic changes over time, as quantification of the changes could well be determined by factors other than a spill from one diagnosis to another. While proportional changes for the broad psychotic groups were minor (3% to 6%, as noted above) more marked proportional changes for sub-groups were apparent. Thus, we described a near doubling in first admissions, and a near tripling in readmissions, in the proportions of 'mania' to 'paranoid schizophrenia' diagnoses over the three periods. While clearly suspicious of spillage from the latter to the former over the study

period, that phenomenon cannot be claimed to have been proved. If consistency across the first admissions and readmissions can be held to support a firm diagnostic change, then spillage is most likely to have occurred from the 'paranoid' and 'remainder' schizophrenias to 'mania', there being no clear suggestion of spill to either of the other two affective sub-groups.

We sought to determine whether the introduction and establishment of lithium might be associated with an increase or decrease in the proportional use of the schizo-affective diagnosis when, as is pointed out in DSM III, there is at present 'no consensus on how this category should be defined' (American Psychiatric Association, 1980). We found little variation over study periods, both for first admissions and readmissions, and suggest that there is no support for the view that the introduction of lithium has been associated with a spill into that category.

Simple correlations demostrated that for schizophrenia, first admissions declined, while readmissions increased over time. By contrast, for the affective psychosis group, both first admissions and readmissions increased over time. These changes, in particular those for first admissions, might reflect the introduction of lithium, particularly when the proportion of 'functional psychoses' to total admissions was relatively constant over the study periods, although such a determinant remains only one possible explanation. As diagnoses may change over time, for a number of reasons, we conducted a series of regression analyses to assess the separate influence of lithium and time, after mutually adjusting for the influence of the other. As lithium and time were so strongly confounded in many of the analyses, separation of the two effects may well have been interfered with by the problem of multicollinearity. In other words, the reason why lithium and time might be insignificant (while generally being significant as single predictors) is that, after adjustment for the other variable, each had almost no residual explanatory power on the admission frequencies. We suspect, but cannot claim as proved, that lithium is the more likely of the 'lithium-time' pair to be the influence on diagnostic patterns. Another possible reason for the difficulty in separating the two effects is that the sample size (at least, the number of years of data) is quite small. For first admission diagnoses of schizophrenia, the coefficients for both time and lithium were not significant, while for readmissions, there was a significant increase in schizophrenia diagnoses over time, after adjusting for lithium, but any lithium effect failed to achieve significance. Pursuing our suspicion that there had been a selective spill from the 'paranoid' schizophrenia sub-group,a similar regression analysis was conducted, showing that lithium was associated significantly with a reduction in the numbers of that diagnosis, after adjusting for any influence of time, both for first admissions and for readmissions. Thus we conclude that the introduction of lithium has not been clearly associated with any change in the overall diagnosis of schizophrenia, but has been associated with a reduction in the diagnosis of paranoid schizophrenia.

For the affective psychosis group, the introduction of lithium was shown to be associated with significant increase in that overall diagnosis for first admissions, and there was a similar trend for readmissions, when the influence of time was effectively controlled. The data for the 'mania' subgroup were analysed in two slightly different ways. In two analyses, the independent variables were affective psychosis and lithium, and lithium was found to be a significant predictor of increased readmissions, but not of first admissions. In two further analyses, total schizophrenia numbers were added as a third independent variable, effectively adjusting for that variable, since significant relationships had previously been demonstrated between lithium and those overall diagnoses. Lithium remained a significant predictor of increased first admissions and increased readmissions for mania.

Thus the introduction and increase in the use of lithium has been associated with a significant increase in the use of the diagnosis of mania, and with a reduction in the use of the diagnosis of paranoid schizophrenia. Such findings would suggest a spill from the latter to the former, but proof cannot be claimed from the present study design, and would require a longitudinal examination of case records of readmitted patients. A rather ironic point might be made here. As noted earlier, Symonds & Williams (1981) argued that the introduction of such an effective treatment as lithium should result in a profound decrease in admissions of those with mania. Thus it is likely that any spill, as a consequence of diagnostic change, is likely to be even greater that suggested by the present data. There are important implications for our finding that the proportion of mania to paranoid schizophrenia diagnoses has increased considerably over the three study periods. If the 'pre-lithium' period ratio had been maintained in the 'established lithium' phase, we calculate that 169 of the first admission patients (as against the 268

observed) and 583 of the readmissions (as against the 1048 observed) would have been diagnosed as having 'mania'. Thus, the changes in diagnosis that we have drawn attention to, and which appear to reflect the impact of lithium being introduced as an effective therapy, are not sterile epidemiological findings, when the effects of diagnosis are recognised as having powerful effects on treatment, on therapists' attitudes, on prognosis, and on treatment.

Acknowledgements

The assistance of Mr W. Simpson-Lee, from the Australian Bureau of Census and Statistics, is noted with gratitude. SDW is supported by a National Health Scientist award from the Canadian National Health Research and Development Program.

References

American Psychiatric Association (1980 *DSM III. Diagnostic and Statistical Manual of Mental Disorders*. Washington: A.P.A.

Baldessarini, R. J. (1970) Frequency of diagnoses of schizophrenia versus affective disorders from 1944 to 1968. *American Journal of Psychiatry*, **127**, 59–63.

Cade, J. F. J. (1979) *Mending the Mind*. Melbourne: Sun Books.

Horgan, D. (1981) Change of diagnosis to manic-depressive illness. *Psychological Medicine*, **11**, 517–523.

Kendell, R. E., Sharpe, L., Cooper, J. E., Gurland, B. J., Gourlay, A. J. & Copeland, J. R. M. (1971) The diagnostic criteria of American and British Psychiatrists. *Archives of General Psychiatry*, **25**, 123–130.

Schou, M. (1983) *Lithium Treatment of Manic-Depressive Illness: A Practical Guide*. 2nd Ed., Basel: Karger.

Symonds, R. L. & Williams, P. (1981) Lithium and the changing incidence of mania. *Psychological Medicine*, **11**, 193–196.

*Gordon Parker, MD, PhD, FRANZCP, *Professor of Psychiatry, University of New South Wales, Randwick 2031, Australia*

Maryanne O'Donnell, MB, BS, *Department of Liaison Psychiatry, Prince of Wales Hospital, Randwick 2031, Australia*

Stephen D. Walter, PhD, *Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*

* Correspondence

(Received 6 March 1984)